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(54) Title: INHIBITORS OF INFLAMMATORY GENE ACTIVITY AND CHOLESTEROL BIOSYNTHESIS

(57) Abstract: Methods of identifying agents effective as inhibitors of short heterodimer protein (SHP) and farnesoid X receptor (FXR) and promoters, cell lines and vectors used in said methods. Methods of preparing and using the agents effective as inhibitors of short heterodimer protein (SHP), including methods of using same to prevent and/or treat a condition associated with inflammatory gene activity and/or cholesterol biosynthesis in a subject. Agents effective as inhibitors of short heterodimer protein (SHP) and farnesoid X receptor (FXR) and compositions comprising same, including compositions effective in reducing inflammatory gene activity and/or cholesterol biosynthesis in a subject.

WO 2003/106632 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18651

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A01N 43/04; C07H 21/04; A61K 31/07

US CL : 514/44, 2; 435/6, 91.1, 325, 375; 536/24.5, 23.1, 24.3, 24.33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44, 2; 435/6, 91.1, 325, 375; 536/24.5, 23.1, 24.3, 24.33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN et al. Nuclear receptor-mediated repression of human cholesterol 7-alpha hydroxylase gene transcription by bile acids. Journal of Lipid Research, 2001 Vol. 42:1402-1412.	1-62, 66 and 67
Y	PARKS et al. Bile Acids: Natural Ligands for an orphan nuclear receptor. Science, 1999 Vol. 284:1365-1368	1-62, 66 and 67
Y	GOODWIN et al. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LXR-1 represses bile acid biosynthesis. Molecular Cell, 2000 Vol. 6:517-526.	1-62, 66 and 67
Y	TU et al. FXR, a bile acid receptor and biological sensor. Trends in Cardiovascular Medicine, 2000 Vol. 10:30-35	1-62, 66 and 67
A,P	LAI et al. Estrogen receptor alpha regulates expression of the orphan receptor small heterodimer partner. Journal of Biological Chemistry, 02 JULY 2003 Vol. 278:36418-	1-62, 66 and 67
A,P	CUI et al. Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. Journal of Biological Chemistry, 13 JANUARY 2003 Vol. 278:10214-10220.	1-62, 66 and 67
A,P	US 2003/0083484 A1 (CROOKE et al) 01 May 2003 (1.5.2003), see claims.	1-62, 66 and 67

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 November 2003 (13.11.2003)

Date of mailing of the international search report

10 DEC 2003

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INTERNATIONAL SEARCH REPORT

PCT/US03/18651

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 03/044167 A2 (ISIS PHARMACEUTICALS,INC.) 30 May 2003 (30.5.2003), see claims.	1-62, 66 and 67

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18651

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 63-65
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 63-65 could not be searched because they contain specific SEQ ID NOs. where no CRF or Sequence Listing was filed with the instant application.
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/18651

Continuation of B. FIELDS SEARCHED Item 3:

EmBase, Caplus, CancerLit, Medline, WEST

search terms: short heterodimer protein (SHP), short heterodimer partner, farnesoid X receptor (FXR), L66, antisense, guggulsterone